BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 34, NO. 10 OCTOBER 1958

THE PATHOLOGICAL EFFECTS OF SMALL DOSES OF RADIATION*

The Fifth Annual Ross Golden Lecture of the New York Roentgen Society

SHIELDS WARREN

Professor, Department of Pathology, Harvard Medical School, Boston, Massachusetts

THE NEW YORK ROENTGEN SOCIETY is most gracious in making me an honorary member and in granting me the distinction of being the first non-radiologist to give this lecture in honor of Dr. Ross Golden, whom I am happy to count among my friends.

Dr. Golden, whose life reaches back into the earlier days of radiology and to whom the radiologists of the present day owe much for his advancement of knowledge and prestige for the profession, was born in 1889, six years before Roentgen discovered x-rays. He, fortunately, is one of the radiologists who has lived beyond the life span of average men and demonstrates that this important profession can be practiced with safety as well as satisfaction.

Radiology early attracted alert and adventurous pioneers who placed the welfare of their patients above their own safety not realizing in the

* Presented at the meeting of the New York Roentgen Society, January 20, 1958, at The New York Academy of Medicine.

early days of the science that safety could be obtained without loss of effectiveness in diagnosis or therapy. Three hundred and two workers in the fields related to medical radiology have lost their lives as a result of the occupational hazards; 197 of these were listed in 1938 on the monument at St. George's Hospital in Hamburg. As medical utilization of ionizing radiation increased, so interest in its biologic effects increased. Pioneer observations demonstrated the effect of radiation in slowing or inhibiting mitosis, producing degenerative changes in cells, both cytoplasm and nucleus, and producing various degrees of injury or necrosis in tissues and organs. The varying sensitivity of the body's cells became apparent within a few years after the discovery of radium and x-rays and by 1910 there was a fairly large, though not generally recognized, pool of knowledge as to radiation effects.

The work of many practitioners and investigators in this country and abroad rapidly advanced the techniques of diagnostic radiology and radiation therapy. Serious attention, however, was not paid for some time to the hazards of radiation, damaged fingers, skin cancer and other disabilities among radiologists, radiologic technicians and radium chemists being regarded as incidental sacrifices to the care of patients. However, the development of better means of detection and measurement of radiation here and abroad, the interest of physicists in radiation and biologic problems led to a clearer understanding and definition of the problems and means of radiation protection. The pioneer work of Failla, Duane, Sievert, Lacassagne, Rock Carling, Regaud, to mention only a few of many, began to call the attention of radiologists and manufacturers of radiation equipment to the need for protection. In the United Kingdom, the first radiation protection committee was established in 1921. The need for their work was further demonstrated by the tragic and vivid experience of the radium dial painters studied so effectively by one of your colleagues, Dr. Martland. A gradually increasing awareness developed throughout the profession that ionizing radiation, although dangerous, could be handled safely. In 1931 a committee established largely through the initiative of the radiologic societies formulated the first code for radiation protection and established a maximum permissible dose of 60 r per year. This followed by almost 30 years the advice of Rollins, one of the pioneers in this country, that the dose should be kept to a dose now thought to be equivalent to 10 r per day.

Today, both the National and the International Committee on Radiation Protection have reduced the permissible dose level to 5 r per year, largely based on the much higher proportion of the population that has entered the atomic energy field. The total number of individuals potentially exposed to radiation is now so large that the older permissible levels might well have added too great a genetic load to our racial pool of mutation. In practice today, as Braestrup's recent study has shown, the actual level of exposure may be as little as 1 r per year. Braestrup believes that radiologists in practice in the early days may have received as much as 100 r per year. Levels acceptable from the standpoint of genetic risk are eminently acceptable from the standpoint of the somatic risks.

While radiologists in recent years have devoted great efforts to preserving the life and health of their patients, there had not been as much attention paid to the protection of themselves and the protection, from the genetic standpoint, of the gonads of their patients.

The widespread public concern with radioactive fallout from atomic weapons tests and potentially from atomic industrial installations led to the formation of the groups both here and in the United Kingdom which issued the National Academy of Sciences reports and the British Medical Research Council report on radiation hazards and also led to the establishment of the United Nations Scientific Committee on the Effects of Atomic Radiation whose report will be published during June this year.

The concern of these groups in determining the sources of genetic exposure to radiation particularly led to the conclusion that aside from natural background in both this country and the United Kingdom incidental exposure of gonads in the course of diagnostic radiologic procedures was the greatest single hazard. Radioactive fallout thus far has contributed only 1 or 2 per cent additional to the natural background radiation. The radiologic societies have taken a very active part in reducing gonadal exposure and this society in particular has been most alert and is helping the New York Academy of Sciences Committees on Radiation Effects to evaluate the practicality of individual exposure records.

It is worth remembering that radiology has moved very rapidly in recent years. It is an index of the rapid progress being made in radiography that the roentgen as a standard unit of measurement was accepted just over a quarter of a century ago. Information as to the biologic effects of an injurious nature caused by both acute and chronic radiation has been well pointed out in the classic articles of Cantril and Sir Stanford Cade. Some of you may recall the November issue of CA with its vivid picture of the hands of Dr. George Pfahler and one of his young radiologic patients.

The pathologic effects of all types of ionizing radiation are essentially the same, variations in those effects being caused by the amount of energy, time of delivery and degree of penetration of the radiation. In the case of unfiltered radium the effect is in close proximity to the radium, as a cutaneous burn if applied externally or necrosis, necrobiosis or neoplasia wherever it may be deposited in the tissues, as demonstrated so brilliantly by Martland. In the case of soft x-rays the more superficial tissues irradiated show radiation damage. In the case of penetrating x-rays, such as those of one to two-million volts, and the energy from linear accelerators and atomic reactors, the skin is no longer the tissue most susceptible to damage but the more radiosensitive tissues anywhere in the field of radiation are predominantly affected. When poorly penetrating and localized radiation is given in small and repeated doses, it tends to produce skin cancer or more rarely sarcoma of the underlying cutis; if the radiation penetrates beneath the skin and reaches large portions or all of the body, the effect may be manifest through the induction of leukemia or shortening of life span. Leukemia has been demonstrated by March, Ulrich and others to be more prevalent in radiologists than in other practitioners of medicine and than the general population. The studies of the survivors of the atomic bombing of Hiroshima and Nagasaki indicate three important effects: 1) that a single dose of radiation may be effective in producing leukemia; 2) that initially at least only a small part of the heavily exposed population (less than 2 per cent) develops leukemia; and 3) that there appears to be a wave of increased incidence of leukemia between 5 and 10 years after a single relatively heavy whole body exposure. Radiation induced leukemia appears to be of any type and its frequency distribution tends to follow that seen in the general population. Faber has just reported on an interesting study on the incidence of leukemia in Denmark following therapeutic and diagnostic radiation. Eighteen per cent of the patients with chronic lymphatic leukemia gave a history of previous radiation as did 30 per cent of chronic myeloid leukemia patients.

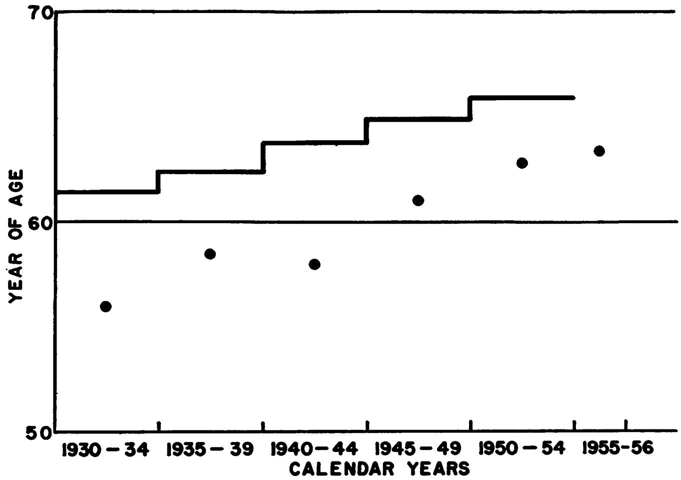
Thirty-two per cent of the cases of acute leukemia had had previous irradiation. This study further showed that particularly in the case of myeloid and acute leukemias such as radiologic diagnostic procedures as had been carried out centered on the thoracic cavity and the abdomen. Faber's study was limited to leukemias occurring in those patients who died over the age of 40 years.

There is statistical evidence from all over the world that leukemia appears to be increasing, perhaps because of better diagnosis, in part because of increased exposure to toxic leukemogenic substances of various sorts, such as benzol, perhaps due to increased use of radiation. Court Brown demonstrated that the x-ray treatment of ankylosing spondylitis led to an increase in leukemia in the patients treated, roughly proportional to dose. Some have even made the unwarranted assumption that leukemia is due to a somatic mutation and that the induction of leukemia is linear in relation to dose. Others, including myself, believe that there is a threshold for the induction of leukemia, and I might even speculate that that threshold for adults lies between 50 and 100 r. The increased incidence of leukemia in children who had been irradiated *in utero* in the course of x-ray pelvimetry of their mothers indicates that the threshold may be lower in infants than in adults. This would be in accord with other observations on radiation effects and indeed some pharmacologic effects.

One of the handicaps in resolving this problem of threshold as against linearity of response with dose hinges on the fact that at low dose levels there may be greater biologic variation in the responses of either humans or test animals than can be detected in experiments. Our currently available evidence in man indicates that the total dose required for the induction of leukemia is large, probably on the order of several hundred rem.* However, even heavy doses approaching the lethal range fail to produce leukemia in many persons.

The stimulus to the study of the chronic effects of radiation provided by the advent of atomic energy and the much wider availability of radioactive substances has led to a number of animal experiments on the effect of varying dose levels on mortality and life span. Many investigators, notably Blair and his associates, have demonstrated life shortening in animals induced by exposure to ionizing radiation. Hardin

* Derived from the initials of *roentgen equivalent man* which, as defined by the International Committee for Radiologic Units, means the dose of ionizing radiation delivered to man and corrected by the relative biologic efficiency factor for the particular type of radiation that happens to be used.



(From Warren, *Klinische Wochenschrift*)

Figure 1.

Jones has marshalled the evidence applicable to man, and suggests that, dealing with the whole population, 1 r of total body radiation substracts 15 days from life span. He points out, however, that other risks than radiation are prevalent. Failla has estimated from experimental and clinical data that the life shortening may be 1.1 day per r. When we think of the many venerable members of the profession of radiology, it seems difficult to accept the idea of life shortening among the members of this profession. However, the experimental evidence is very strong, and I wish to present to you a refinement of the earlier data that I have obtained from the obituary columns in the Journal of The American Medical Association. Figure 1 shows in heavy lines the average age of the male population of the United States over 25 years of age, grouped by calendar quinquennia. This is represented by the heavy lines and shows a steady improvement over the years. I chose over 25 years of age for comparison because few below that age practice radiology. The average age at death of radiologists as taken from the columns of the Journal of The American Medical Association is presented in the form of dots and illustrates that radiologists as a group die five years earlier than the corresponding male population over 25 years of age, but that improvement in longevity of radiologists is demonstrated. This improvement has been particularly marked since

World War II when, thanks to the atomic age, concepts of radiation protection were both more sharply defined and more widely diffused through the population. This life shortening is not due to specific occupational diseases, such as leukemia or skin cancer, but rather to a non-specific effect that might be characterized as premature aging. Thus, whether the cause of death is coronary occlusion, cancer, bronchopneumonia or nephritis, the radiologist on the average is younger than his counterparts among his non-radiologic colleagues or the adult male population. This non-specific effect may be related to almost imperceptible changes in fibrous and elastic tissue and to impairment of mechanisms of immunity. Still further work needs to be done to insure such sound protection or counteraction of effects that the radiologist is not only safe from local injury, skin cancer or leukemia, but safe from subtle generalized injury as well.

I mentioned early in the course of this address that genetic factors were of importance in determining the levels of radiation protection. What data have we on the effects of radiation, either acute or chronic, on the children of irradiated parents to compare with the rather abundant but as yet inadequate mass of information on animals? Because of the clear understanding of its genetic characteristics, the short time period of its generations and the large size of its chromosomes, the fruit fly has been a favorite tool of geneticists. Less work has been done with the mammal. However, the work of Russell on mice indicates that this warm-blooded mammal is, if anything, more sensitive from the genetic standpoint to ionizing radiation than is the fruit fly. Studies on the heredity of man are difficult because of the long span of his generations and because of the complexity of his hereditary patterns. In general, we can assume that a significant proportion, probably less than half, of the mutations carried by man at the present time are due to the background radiation that his germ plasm has received through the course of his development.

The number of genes in man is probably somewhere between 200,000 and 800,000, although this rests on a none too strong foundation. It is clear that radiation induces mutation and that the effect is both cumulative and linear. There exist three studies in man which I believe to have significant bearing on this important point. The survivors of a single dose of acute radiation ranging from just sublethal to just above background have been studied carefully in Hiroshima and Nagasaki by Neel and Schull. They have demonstrated that in the first generation, where one or both parents had been exposed to radiation from the atomic bomb explosion, there was no significant increase in mutations over the control population. However, the figures are insufficient in number to prove there was no effect. The likelihood is strong that a slight effect did exist.

Macht and Lawrence in 1955 made a questionnaire study based on 2236 radiologists with children. There was an average of 2.69 children per radiologist, a total of 6007. Six per cent of the children with radiation-exposed fathers showed hereditary defects, whereas 4.8 per cent of the children with unexposed fathers had defects. This difference is too narrow to accept as being significant.

Crow, the same year, compared fetal and infant death rates in the progeny of radiologists and pathologists. The wives of radiologists had 16.6 per cent stillbirths and miscarriages. The wives of pathologists had 15.9 per cent, no significant difference. The infant mortality rates in the two groups were also not different but the numbers were very small. On the basis of available studies, therefore, we can assume that there is probably not a significant difference in the incidence of first generation effects in the progeny of radiologists and non-radiologists. However, extensive second generation studies will be necessary before we can assume that man is an exception to the rule and does not show evidence of genetic damage following absorption of radiation by the gonads.

In summary, we may say that cancer of superficial tissues is no longer a hazard to the radiologist; that leukemia apparently is a hazard but may be minimized by adherence to the present standards of protection; that shortening of life span is a hazard, but that this is rapidly being eliminated by current standards of protection; that we may expect man, including radiologists, to follow the same laws of transmission of hereditary characteristics as other mammals; and that the present rules for protection reduce the exposure risks to acceptable levels.